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Mini review:

MANAGING POST STROKE HYPERGLYCAEMIA: MODERATE GLYCAEMIC CONTROL IS BETTER? AN UPDATE

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ABSTRACT

Post stroke hyperglycaemia (PSH) is prevalent in acute ischaemic stroke (AIS) patients and it has been associated with a dismal outcome of death and disability. Insulin has been proven to attenuate glucose effectively in stroke patients, thus many trials over the years had studied the efficacy of intensive treatment aiming at normalization of blood sugar level in order to improve the bleak outcomes of PSH. However, tight glycaemic control failed to be translated into clinical benefits and the outcomes are no different from the conventional approach, despite the costly healthcare expenditure invested. On the contrary, it brings more significant harm than the intended benefit, as 1 in every 9 treated patients had symptomatic hypoglycaemia. Thus, the benefits of tight glucose control, if any, are overshadowed by this potential risk of hypoglycaemia causing permanent neurological injury. Therefore, international practice guidelines recommend for less aggressive treatment to maintain blood glucose level within an appropriate range in AIS patients. However, there are limited details for stroke-specific glycaemic management and this made management of PSH particularly difficult. This review is to discuss and provide suggestions concerning glycaemic control in acute ischaemic stroke; the direction of its future prospective clinical trials and the treatment strategy required based on recent literature.

Keywords: Acute ischaemic stroke, hyperglycaemia, glycaemic control, insulin

INTRODUCTION

Almost 2 in every 3 acute stroke patients have elevated blood glucose more than 6.1 mmol/L at presentation, reflecting the alarmingly high prevalence of post stroke hyperglcaemia (PSH) in acute ischaemic stroke (AIS) populations (Scott et al., 1999b). In recent years, there has been much discussion over the possible mechanisms of hyperglycaemia causing ischaemic brain injury. It has been postulated that hyperglycaemia is associated with impaired recanali-

zation (Ribo et al., 2005), decreased perfusion (Quast et al., 1997), increased reperfusion injury (Kamada et al., 2007) and cerebral lactic acidosis secondary to mitochondrial dysfunction (Anderson et al., 1999).

In AIS, the prognostic influence of glycaemia level is evident. Whether PSH is the result of uncontrolled diabetes or newly diagnosed diabetes, or merely a physiological stress response, it is an important independent prognosticator of stroke mortality in AIS patients (Capes et al., 2001; Weir et al., 1997). These hyperglycaemic stroke patients are susceptible to have a larger cerebral infarct with subsequent worsening of neurological disabilities (Parsons et al., 2002). Admission hyperglycaemia is found to increase the risk of death by 2.3 times in AIS patients (Stead et al., 2009). Likewise, morbidity of AIS patients with persistent hyperglycaemia more than 8.5 mmol/L was found to be 3 times more than normoglycaemic stroke patients (Fuentes et al., 2009).

In spite of the fact that early and persistent inpatient hyperglycaemia causing poor outcome, there is still no consensus on the specific management of hyperglycaemia in AIS, as opposed to hyperglycaemia in non-stroke acute illnesses (Quinn et al., 2011). The effect of hyperglycaemia to the brain is different than peripheral tissues as its glucose metabolism is more complex and the energy consumption is higher (Pakhetra et al., 2011) Furthermore, the insulin receptors in the brain are structurally and functionally different from the peripheral receptors, as they have insulin-independent means of obtaining glucose and the ability to modulate neurotransmitter function. Their role in the function and development of central nervous system (CNS) is more than just regulation of glucose utilization (Schulingkamp et al., 2000).

In light of the foregoing, this review will highlight on the complex relationship between hyperglycaemia and ischemic stroke, addressing controversial issues such as target and glycaemic control and its association hypoglycaemic complication and monitoring, as well as treatment strategies such as route, timing and duration of therapy.

GLUCOSE-LOWERING THERAPY: WHAT AND HOW TO START?

Oral glycaemic control agents are not recommended for treatment of PSH due to the danger of hypoglycaemia and acidosis when used in acutely ill patients, especially in dysphagic stroke patients (Baker et al., 2011). Instead, insulin is the preferred treatment for several reasons. First, the therapeutic efficacy of insulin treatment for PSH is proven to reduce the glucose level in AIS patients (Bellolio et al., 2014; Laird and Coates, 2013). Second, intravenous or subcutaneous insulin is easier to administer on stroke patients, especially those with swallowing difficulties and reduced conscious level. Third, insulin also promotes an activity of endothelial nitric oxide (Cleland et al., 2000) and has an immune-modulatory effects that may control the infarction size which subsequently improve the prognosis of PSH patients (Marik and Raghavan, 2004; Hamilton et al., 1995).

As compared to subcutaneous insulin regime, intensive intravenous insulin lowers blood glucose more significantly in the first hours of stroke presentation. However, AIS patients treated with intensive insulin therapy are 18 times more likely to have hypoglycaemia (Bellolio et al., 2014). Moreover, hypoglycaemia in AIS patients might be more harmful than in non-stroke patients as it can cause deleterious neurological outcomes (de Courten-Myers et al., 1994; Zhu and Auer, 2004), but the exact glucose value that can be considered dangerously low is still unascertained (Kruyt et al., 2010). Hence, recent American stroke guideline recommends the use of subcutaneous insulin, as the risk of hypoglycaemia is less. Subcutaneous insulin with basal insulin regimes can usually maintain appropriate normoglycaemia in most AIS patients (Bruno et al., 2010). In addition, monitoring and administering of meal

subcutaneous insulin sliding scale is simpler i.e. only four times a day as compared to rigorous hourly glucose monitoring for intravenous insulin infusion therapy. A simple weight based subcutaneous insulin basal bolus regimens, along with insulin sensitivity factor should be used when calculating the insulin dosing to achieve better glucose control (Baker et al., 2011).

Nevertheless, if the hyperglycaemia is persistently more than 11.1 mmol/L, intravenous insulin infusion may be used with frequent glucose monitoring (Jauch et al., 2013). Since there are several sliding scale protocols available, the choice depends on familiarity and availability of health resources, and safety in term of appropriate adjustments in case of hypoglycaemia events. In special circumstances such as type 1 diabetes mellitus, diabetic ketoacidosis, hyperosmolar state or difficult nutrition regimens, an endocrine consultation is necessary for an optimum management (Baker et al., 2011).

Besides hypoglycaemia as the major adverse effects of insulin therapy, hypokalaemia can also occur as insulin causes extracellular shift of potassium into the cells (Radó, 1989). In spite of this, no significant hypokalemia was reported in two trials using intravenous insulin (Bruno et al., 2008; Walters et al., 2006). The usage of intravenous infusion of glucose-potassium-insulin (GKI) solution is intended to be more physiological in reducing the glucose level and maintaining potassium level. Several randomised controlled studies that have used GKI in their treatment arm found that GKI solution was beneficial and safe to be administered to AIS patients with mild to moderate PSH, although evidence on the clinical gain is not significant (McCormick et al., 2010; Scott et al., 1999a; Gray et al., 2007).

In short, the possible options of inpatient glucose lowering protocol in PSH are subcutaneous insulin or intravenous insulin or GKI infusion solution. It depends on the severity of hyperglycaemia, the risk of hypoglycaemia and the availability of labour and healthcare resources. Regular monitoring of the blood glucose and electrolytes is essential in order to avoid the complication of hypoglycaemia and hypokalemia from insulin therapy.

WHEN TO START TREATMENT?

The current recommendation of international guidelines regarding ischaemic stroke patients, is blood glucose should be maintained within the normoglycaemic range (Baker et al., 2011; Jauch et al., 2013; Intercollegiate Stroke Working Party 2012). But the exact glucose value by which insulin treatment should be initiated is unclear, since different studies used different cut-off values of hyperglycaemia.

Data analysed from the Virtual International Stroke Trials Archive (VISTA) (Ali et al., 2007), an established central stroke database, reported a 12.9 % increase in mortality and poor functional outcome among stroke patients with glucose levels of more than 7 mmol/L for 48 hours (Muir et al., 2011). The Glycemia in Acute Stroke study (GLIAS) and also large scale study done on 960 AIS patients showed similar poorer outcome in stroke patients with higher cut-off glucose value i.e. 8.6 mmol/L and 8.2 mmol/L respectively (Gentile et al., 2006; Fuentes et al., 2009).

It is still unclear when to start insulin treatment during PSH, though early initiation time may be beneficial. In a study on PSH patients with normalization of glucose during initial 48 hours of admission, the risk of death is reduced by 4.6 times compared to those with persistent hyperglycemia (Dziedzic et al., 2010). A study from VISTA databases showed those AIS patients who received insulin treatment at a median 5.5 h after admission had a better prognosis at 90 days (Muir et al., 2011). In addition, the practicability and safety of rapid corrections of hyperglycaemia with intravenous insulin during AIS has also been shown in other clinical trials (Bruno et al., 2008; Johnston, et al., 2009; Kreisel et al., 2009). Nonethe-

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less, in hyper-acute stroke presentation (< 6 hours), intensive intravenous insulin should be used with caution as a study had linked it with infarct growths (Rosso et al., 2012).

In summary, the definitive timing and glucose value at which insulin treatment should be initiated remain to be determined, although earlier initiation from the first 24 to 48 hours after admission is practical and may be beneficial (Jauch et al., 2013; Baker et al., 2011).

DURATION OF TREATMENT: 24, 48, 72 HOURS OR > 5 DAYS?

In relation to the duration of insulin therapy, no guidelines are available. For subcutaneous insulin regimens, the ideal practice is to continue the inpatient treatment to outpatient care, with a reduction of 10 to 20 % dosage to prevent hypoglycaemia. As for intravenous insulin infusion, different trials of acute glycaemic intervention in PSH used different durations of treatment, ranging from 1 to 5 days.

A study by Walters MR et al. (2006) found 48 hours duration of insulin infusion was sufficient and treatment more than 48 hours was unnecessary. In addition, VISTA and GLIAS study found that hyperglycaemia within initial 48 hours was associated with higher mortality (Fuentes et al., 2009; Muir et al., 2011). On the contrary, shorter 24-hour insulin duration as in GIST-UK study did not show any significant clinical impact.

In regard to hypoglycaemia risk, there was no association between longer duration of treatment and hypoglycaemia. For instance, GRASP which has 5 days duration of treatment as compared to THIS trial, with a 24-hour duration of treatment, had similar incidence of hypoglycaemia in the intensive insulin treatment group. Therefore, even a short duration of insulin treatment can result in hypoglycaemia, with rate as high as 71 % (Kim et al., 2009).

To conclude, 48 hours of intravenous insulin treatment appears to be the optimal duration and should be used as the intervention duration in future trials.

GLUCOSE LEVEL: WHAT LEVEL TO ACHIEVE?

International practice guidelines recommend for less aggressive insulin treatment to maintain blood glucose level within an appropriate range in AIS patients. However few recommendations are provided for stroke-specific glycaemic management and this made management of PSH complicated. The aggressiveness of glucose management control in stroke patients varies according to physician specialty groups (Casaubon et al., 2008).

The recently updated Cochrane systematic review in 2014 had analysed 11 randomised controlled trials (RCT) of insulin treatment for PSH in diabetics and non diabetics patients, with narrow target blood glucose of 4 to 7.5 mmol/L, looking at dependency or death at 1 month or 3 month as the primary outcome (Bellolio et al., 2014). The review had updated 3 new RCTs but the results are unchanged from the previous first review in 2011 (Bellolio et al., 2011). Again, it concluded that tight glycaemic control failed to be translated into clinical benefits, as the outcomes are no different than conventional approach, despite the costly healthcare resources invested. In fact, it brings more significant harm than the intended benefit, as 1 in every 9 treated patients had symptomatic hypoglycaemia. The possible benefits of controlling tight glucose levels, if any, are overshadowed by this potential risk of hypoglycaemia causing permanent neurological injury.

For this reason, AHA/ASA 2013 guidelines suggested that it is practical to treat PSH by maintaining blood glucose levels in a range of 7.8 to 10.0 mmol/L in all hospitalized patients (Jauch et al., 2013). European stroke 2012 guidelines also has a similar suggestion but with a broader range of 4 to 11 mmol/L target blood glucose (Intercollegiate Stroke Working Party, 2012).

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Until further clinical trials establish the efficacy and the risk-benefit ratio of rapid hyperglycemia correction during AIS, a loose glycaemic target should be encouraged in order to avoid hypoglycemia and excessive resource that is associated with its prevention and monitoring in PSH. Perhaps the current much anticipated on-going SHINE trial will provide a clear lead to this controversial PSH management (Bruno et al., 2014).

MORE ABOUT HYPOGLYCAEMIA

Hypoglycaemia in stroke patients most commonly occurs when glucose lowering treatment is instituted and rarely occurs spontaneously. There are no unified definitions of hypoglycaemia in AIS (Bruno et al., 2008; Gray et al., 2007), though in practice, the diagnosis of hypoglycaemia is usually by the Whipple's triad (Cryer et al., 2009). Since the clinical manifestations are sometimes non specific (McAulay et al., 2001), documentation of abnormally low blood glucose with the event of hypoglycaemia is valuable in diagnosis (Baker et al., 1997). American Diabetes Association proposes cut-off values of less than 3.9 mmol/L and further classification depends on the glycaemia values and its associated symptoms (American Diabetes Association Workgroup on Hypoglycemia, 2005). Low glycaemic values of 2.8 to 3.9 mmol/L are typically considered mild hypoglycaemia if patients are asymptomatic and moderate hypoglycaemia if patients have autonomic symptoms such as tremors and sweating. Lower glycaemic values less than 2.2 to 2.8 mmol/L with neurological dysfunction symptoms are regarded as severe hypoglycaemia (Baker et al., 2011; Cryer et al., 2003). However, in patients with diabetes, the threshold value for glucose level of symptomatic hypoglycaemia is higher (3.9 mmol/L) than in non-diabetes patients (3.0 mmol/L) (Desouza et al., 2010; Cryer et al., 2009). This is an important factor, as most studies on tight glycaemic control in AIS, did not consider whether the hypoglycemia is harmful to the patients or not.

Different studies used different cut-off values ranging from < 3.0 to < 4.0 mmol/L, but the recent Cochrane systematic review uses glucose level less than 3.0 mmol/L and the patients are further classified into symptomatic or asymptomatic hypoglycaemia (Bellolio et al., 2014). The chosen cut-off point will have a significant impact on the number of reported cases of hypoglycaemia. Therefore, for future studies that includes diabetic stroke patients, standardised definition of hypoglycaemia is needed and should be set lower than the definition of 3.9 mmol/L (Swinnen et al., 2009).

Proper management of hypoglycaemia is crucial as prolonged untreated hypoglycaemia can result in permanent neurological injury and even death. Once hypoglycaemia is identified in AIS patient, it should be treated urgently with dextrose solution, preferably 25 mL of 50 % dextrose given in slow intravenous push (Jauch et al., 2013).

FUTURE TRIALS

Several factors need to be taken into account when initiating future clinical trials. First, most studies in this review that included both diabetic and non-diabetic AIS patients, revealed conflicting mortality outcomes between them. A large meta-analysis of 32 cohort studies concluded that in PSH, non diabetic patients have worse mortality and functional outcome than diabetic patients (Capes et al., 2001). A lower value of cut-off glucose level of 6.3 mmol/L in non-diabetic patients is associated with early fatality, as compared to 10.3 mmol/L in diabetic patients, according to another study (Farrokhnia et al., 2005). In terms of intensive treatment with intravenous insulin, on the contrary, a systematic review of 11 studies found no difference in outcome between patients with diabetes mellitus and without diabetes mellitus (Bellolio et al., 2014).

Second, all studies did not differentiate between lacunar and cortical stroke in their

inclusion criteria and this may attribute to conflicting result. Initial studies in animals with lacunar infarcts had reported beneficial effect of hyperglycaemia and aggressive treatment (< 7 mmol/L) was proven harmful (Ginsberg et al., 1987; Prado et al., 1988). Likewise, a recent clinical study done on 1375 ischaemic stroke patients also found that moderate PSH of 8.0 to 10.0 mmol/L in lacunar infarct resulted in favourable outcome, independent of stroke severity, diabetes and age (Uyttenboogaart et al., 2007).

Third, post-hoc analysis of GRASP study did show the probability of good functional outcome with five days of tight glycaemic control of 3.9 to 6.0 mmol/L with insulin treatment (Johnston et al., 2009). The shorter 24 hours to 48 hours duration of treatment used in most clinical trials probably is not sufficient to improve outcomes as the clinical benefit of glucose lowering therapy is probably maximized when treatment is continued for at least 2 to 3 days beyond the acute initial 24 hour stroke presentation (Kruyt et al., 2010).

Hence for future clinical trials, it is recommended that firstly, longer duration of glycaemic control be required to assess the efficacy of insulin treatment. Secondly, comparison of PSH outcomes between early and late insulin intervention with the effect of time to euglycaemia should be considered. Lastly, selecting non-diabetic patients and non-lacunar infarct might enhance the chances of finding a treatment effect for glycaemic control in PSH.

CONCLUSION

The management of hyperglycaemia in acute stroke should evolve towards less rigorous glycaemic control, as compared to the previous practice of tight glycaemic control. In spite of the numerous studies done, evidence is still inadequate to determine the judicious hyperglycemia management practice in AIS setting. At present, there is no conclusive clinical evidence that tight glycaemic control during acute ischemic stroke is the right approach, as it does not elude the possibility of death or disability.

While we wait for findings from current and future clinical researches, the recommended approach in the management of PSH is to balance the therapeutic benefit of insulin treatment with the potential harm of hypoglycaemia. Taking into consideration the manpower, expense and risk involved in a timely and safe correction of hyperglycaemia in AIS, less aggressive treatment with subcutaneous insulin is recommended to ensure optimal outcomes.

Disclosure of Conflicts of Interest

I certify that all my affiliations with or financial involvement in, within the past 5 years and foreseeable future, any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript are completely disclosed.

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